REMARKS

I. The Invention

The present invention resides in the novel strategy of *ex vivo* preparation of a tumor-specific vaccine based on the use of bispecific antibodies, which are heterologous intact antibodies of certain isotype and subclass combinations. By virtue of its specificities for a tumor-associated antigen, a T cell receptor, and an Fc receptor, a bispecific antibody of the present invention simultaneously binds to a tumor cell (an autologous tumor cell that is extracted from a patient and bears a tumor-associated antigen of endogenous source), a T cell, and an Fc receptor-positive effector cell. An enhanced tumor-specific immunity is achieved following the recruitment of T lymphocytes and Fc receptor-bearing effector cells to the tumor cells and the subsequent activation of the T cells and effector cells.

II. Status of the Claims

Claims 1-26 were originally filed. Claims 27-30 were later added. Upon entry of the present amendment, claims 1-8, 13-21, 23, and 26 remain pending. Claim 1 is amended to recite the isotype combinations of "rat-IgG2b/mouse-IgG2a, rat-IgG2b/mouse-IgG2b, and rat-IgG2b/mouse-IgG3" to replace "rat/mouse," which is supported by claim 27 as originally filed. Claim 27 is canceled. The present amendment adds no new matter.

III. Claim Rejections

A. 35 U.S.C. §103(a) over the Volker, Deo, and Lindhofer References

The examiner maintained the rejection of claims 1-8, 13, 15, 16, 19-21, 23, 26, and 27 under 35 USC §103(a) for alleged obviousness over Volker *et al.* in view of Deo *et al.* and Lindhofer *et al.* Applicants respectfully traverse the rejection, particularly in light of the present amendment and Dr. Lindhofer's Declaration.

1. Characterization of Claim 1 and the Volker, Deo, and Lindhofer References

Claim 1 as amended is drawn to a method for preparing an antibody-tumor cell preparation. The claimed method comprises the steps of (a) isolating autologous tumor cells; (b) treating the tumor cells to prevent post-reinfusion survival; and (c) incubating the treated tumor cells with intact heterologous bispecific antibodies capable of: (i) binding to a T cell; (ii) binding to at least one tumor-associated antigen on a tumor cell; (iii) binding to an Fc receptor-positive cell via the Fc portion; and (iv) activating the Fc receptor-positive cell whereby the expression of cytokines, co-stimulatory antigens or both is induced or increased. The bispecific antibodies are further limited to the isotype combinations enumerated in claim 1, including rat-IgG2b/mouse-IgG2a, rat-IgG2b/mouse-IgG2b, and rat-IgG2b/mouse-IgG3, which are imported from claim 27 as previously presented.

The Volker *et al.* reference discloses methods for inducing an enhanced anti-tumor immunity and for producing a tumor-specific vaccine. These methods require the initial step of antigenizing the tumor cells with an antigen of exogenous origin, *e.g.*, viral protein hemagglutinin-neuraminidase (HN) expressed on the tumor cell surface following the transfection of the tumor cells with the Newcastle Disease Virus (NDV). A bonding agent with dual-specificity, one for the exogenous antigen on the tumor cell surface (such as a viral protein) and the other for a molecule on an effector cell surface (such as CD2 or CD3 on a T cell), is then used to bring the effector cell into close contact with the tumor cell and achieve increased immunogenicity of the tumor cells.

The Deo *et al.* reference relates to recombinant multispecific molecules, which comprise an anti-Fc receptor portion and an anti-target portion, as well as the methods for making and using such molecules.

The Lindhofer *et al.* reference discloses methods for generating and purifying bispecific rat/mouse antibodies. Using these methods, one can improve the efficiency of producing functional bispecific antibodies and simplify the process of

purifying the bispecific antibodies. The reference discloses rat/mouse isotype combinations of rat-IgG2a/mouse-IgG2a and rat-IgG2b/mouse-IgG2b.

2. The Elements of Claim 1 Appear to Be Present in the Cited References

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all elements of a claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the elements; and there must be a reasonable expectation of success in making such combination. MPEP §2143.

It appears that the Deo reference provides the three binding specificities of a bispecific antibody recited in claim 1, and the Lindhofer reference provides one rat/mouse isotype and subclass combination, rat-IgG2b/mouse-IgG2b, of claim 1. These three references together do not teach or suggest how to *generally* ensure the capability of a bispecific antibody to activate an Fc receptor-positive cell and lead to the increased expression of cytokines and/or co-stimulatory antigens, even though this property may be inherent in some cases, *e.g.*, for a bispecific antibody of the rat-IgG2b/mouse-IgG2b isotype/subclass combination that has an Fc portion and can bind with specificity to a T cell, a tumor-associated antigen on a tumor cell, and an Fc receptor-positive cell (see more detailed discussion below).

3. The References Fail to Suggest Combining the Elements of Claim 1

Although the elements of claim 1 can be found in the three references, the Examiner has not shown where in the three references one can find a motivation or suggestion to combine these elements. To support the conclusion that "the prior art as a whole appears to teach the claimed inventions," the Examiner merely asserted that Volker *et al.* and Deo *et al.* supply some elements of claim 1 and that "the advantages that Lindhofer teach with respect to purification and high yield would have motivated one of skill in the art to use the antibodies of Lindhofer" (the paragraph bridging pages 3-4 of the Office Action mailed August 26, 2003).

Applicants contend that without more, the Examiner's statements are insufficient to establish *prima facie* obviousness. According to MPEP §2143.01, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." When the three references are viewed together, the Volker and Deo references are silent about the bispecific antibody isotype/subclass combinations; while the Lindhofer *et al.* reference teaches the advantages of bispecific antibodies in antibody production and purification, and further identifies two rat/mouse isotype/subclass combinations for bispecific antibodies, the reference does not indicate that these two particular isotype/subclass combinations are essential for achieving the production and purification advantages. The teaching by Lindhofer *et al.* thus provides at best only a general motivation for one to try bispecific antibodies in antibody production; it does not provide a specific motivation or suggestion to combine Lindhofer's teaching with the disclosure by Volker *et al.* or Deo *et al.*, nor does it necessarily suggest the use of the two particular isotype/subclass combinations.

Most important of all, none of the three references disclose the importance of the isotype/subclass combination of a bispecific antibody in the successful practice of the present invention (see detailed discussion in the next section).

Thus, it has not been shown how one of skill in the art would be motivated to combine the elements of claim 1 based on the disclosure of the Volker, Deo, and Lindhofer references.

4. There Is No Reasonable Expectation of Success

Even if some motivation or suggestion could be found in the cited references to combine the elements of claim 1, Applicants contend that there would be no reasonable expectation of success in combining the elements.

The Lindhofer *et al.* reference describes bispecific antibodies of two isotype/subclass combinations, rat-IgG2b/mouse-IgG2a and rat-IgG2a/mouse-IgG2a. As

Dr. Lindhofer explains in his Declaration, there are various types of Fc receptors and cells bearing these receptors may have very different physiological functions. For example, a T cell and an accessory cell bearing Fcγ receptor type I or III, which is able to phagocytose, tend to achieve costimulation from crosstalk between cell surface molecules of the two cell types. On the other hand, Fcγ receptor type II (also known as CD32) is capable of delivering inhibitory signals and is present on, *e.g.*, B cells, which are unable to phagocytose. Therefore, the recruitment of a T cells and an accessory cell bearing Fcγ receptor type I or III by a bispecific antibody of a suitable isotype/subclass combination may lead to costimulation of the T cell and the accessory cell, whereas the recruitment of a T cell and a Fcγ receptor type II-bearing cell (such as a B cell incapable of phagocytosis) to a tumor cell by a bispecific antibody of a different isotype/subclass combination may not lead to costimulation of the T cell and the Fc receptor-positive cells, and consequently, will not lead to a desired anti-tumor immunity. As such, only a bispecific antibody of an appropriate isotype/subclass combination is effective for inducing an anti-tumor immunity according to the present invention (Paragraph 8 of the Declaration).

With regard to the isotype/subclass combinations of bispecific antibodies used for practicing the present invention, Dr. Lindhofer further states in paragraph 9 of the Declaration,

> If one attempts to use a bispecific antibody of a particular isotype/subclass combination to elicit an anti-tumor immunity according to the present invention, the chance of success cannot be predicted before the antibody is actually made and tested for its efficacy. The Lindhofer *et al.* reference describes bispecific antibodies of the isotype combinations of rat-IgG2b/mouse-IgG2a and rat-IgG2a/mouse-IgG2a without offering any distinction between the two for their usefulness in practicing the method of the present invention. Only through our experiments were we able to determine that rat-IgG2b/mouse-IgG2a is a suitable isotype combination, whereas a rat-IgG2a/mouse-IgG2a

bispecific antibody is not effective for immunizing a patient against tumor cells.

It is therefore clear that even if one of ordinary skill in the art were somehow motivated by the cited references to attempt the invention of the present application by combining the elements of claim 1, there would be no reasonable expectation of success. This is particularly so because nowhere in the three cited references can one find the general teaching as how to engineer a bispecific antibody by choosing a suitable isotype/subclass combination to achieve the co-activation of a T cell and an Fc receptor-bearing cell, the increased expression of cytokines and/or co-stimulatory antigens, and ultimately the anti-tumor immunity.

5. Summary

Although the elements of claim 1 appear to be present in the Volker, Deo, and Lindhofer references, the three references together provide no motivation or suggestion for one to combine the elements of claim 1. Furthermore, even if such a motivation or suggestion were found, according to Dr. Lindhofer, there would be no reasonable expectation of success because of the diversity in the types of Fc receptors and in the functions of Fc receptor-positive cells. The three references do not disclose the importance of isotype/subclass combination for a bispecific antibody.

As such, Applicants submit that a *prima facie* showing of obviousness has not been established. Accordingly, the withdrawal of the rejection under 35 U.S.C. §103(a) over Volker *et al.* in view of Deo *et al.* and Lindhofer *et al.* is respectfully requested.

B. 35 U.S.C. §103(a) over the Volker, Deo, Honsik, and Lindhofer References

The Examiner raised a new rejection of claims 1, 14, 17, and 18 under 35 U.S.C. §103(a) for alleged obviousness over Volker *et al.* and Deo *et al.* in view of Honsik *et al.* and Lindhofer *et al.* Applicants respectfully traverse the rejection, particularly in light of the present amendment.

1. Characterization of Claim 14 and the References

Claim 14 is drawn to a method for preparing a vaccine comprising activated peripheral blood mononucleated cells. This method comprises the steps of: (a) isolating autologous tumor cells; (b) treating the tumor cells to prevent their survival following reinfusion; and (d) incubating the treated tumor cells with an intact heterologous bispecific antibody (which has the properties enumerated in claim 1) and peripheral blood mononucleated cells, thereby activating said peripheral blood mononucleated cells, and preparing a vaccine from the activated peripheral blood mononucleated cells.

Thus, the claim elements to be considered in this obviousness analysis are those of claim 1 plus the element of peripheral blood mononucleated cells. The Examiner indicated that claim 1 was rejected on the same ground because of the open transitional phrase "comprising," which could allow an additional step of introducing peripheral blood mononucleated cells into the antibody-tumor cell preparation.

The Volker *et al.*, Deo *et al.*, and Linderhofer *et al.* references have been characterized in an earlier section.

The Honsik *et al.* reference describes a method for utilizing *ex vivo* IL-2 activation of immune effector cells and arming the activated effectors with monoclonal antibodies whose first binding specificity allows their binding to the effectors and whose second binding specificity allows their binding to an antigen on the surface of the target cells. Honsik *et al.* do not expressly disclose or implicitly suggest an antibody with three binding specificities as recited in claim 1 of the present application.

2. The Elements of Claim 14 Appear to Be Present in the References

The elements of claim 14 appear to be present in the four references cited: as noted above, the Volker, Deo, and Lindhofer references together provide the elements of claim 1; the additional element of peripheral blood mononucleated cells is supplied by the Honsik *et al.* reference.

3. The References Fail to Suggest Combining the Elements of Claim 14

As stated in section III.A.3 of this paper, no motivation or suggestion can be found in the Volker, Deo, or Lindhofer reference for one to combine the elements of claim 1, particularly to adopt the isotype combinations disclosed by Lindhofer *et al.* when making bispecific antibodies used for inducing an anti-tumor immunity. Neither has such a motivation or suggestion been shown in the Honsik reference, even though the Honsik reference provides the additional element of introducing peripheral blood mononucleated cells into an antibody-tumor cell preparation.

4. There Is No Reasonable Expectation of Success

For the same reasons discussed in section III.A.4, even if one of skill in the art would somehow become motivated or suggested by the about-cited references to combine the elements present therein, there still would be no reasonable expectation of success "due to the diversity in the types of Fc receptors and the physiological functions of cells expressing the Fc receptors" (Dr. Lindhofer's Declaration, paragraph 10). This lack of reasonable expectation of success is further due to the lack of teaching in the cited references about the importance of isotype/subclass combination in the present invention.

5. Summary

Although the elements of claim 14 appear to be present in the Volker, Deo, Honsik, and Lindhofer references, the references do not provide a motivation or suggestion for combining the elements. Furthermore, even if one of skill in the art were to combined the elements, there would be no reasonable expectation of success.

Applicants therefore submit that an appropriate case of *prima facie* obviousness has not been established. As such, the withdrawal of the rejection under 35 U.S.C. §103(a) over Volker *et al.* and Deo *et al.* in view of Honsik *et al.* and Lindhofer *et al.* is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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